PATENT SPECIFICATIO

NO DRAWINGS

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COMPLETE SPECIFICATION

Tetrahydropapaverine Derivatives and their preparation

We, Allen & Hanburys Limited, a British Company, of Three Colts Lane, Bethnal Green, London, E.2, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement: -

This invention relates to new heterocyclic compounds.

The compounds of the present invention are diquaternary salts of bis-[ω-(tetrahydropapaverino)alkyl] esters of aliphatic dicarboxylic acids of the general formula:

where R is a lower alkyl group containing not more than 6 carbon atoms; X is an anion; m is 2 or 3 and n is 0, 1, 2, 3 or 4.

The preferred compounds are the di-20 bromide and di-iodide of bis-[γ-(N-methyltetrahydro-papaverino)propyl] oxalate.

The present invention also includes a process for preparing the compounds of the present invention where X is bromine, which 25 comprises refluxing an excess of an N-alkyl tetrahydro papaverine with an ω-bromalkyl dicarboxylate in an inert solvent for a prolonged period, e.g., several days. The inert solvent may, for example, be an aromatic 30 hydrocarbon such as benzene.

The resulting dibromide may be converted by conventional methods, e.g., double decomposition with other diquaternary salts such as the dinitrate and diperchlorate.

The present invention further includes a process for preparing the compounds of the [Price

present invention which comprises reacting an ω-bromoalkyl dicarboxylate with tetrahydro papaverine in the presence of an acid-binding agent, and treating the product obtained with at least 2 molecular proportions of an alkyl halide or sulphate.

The compounds of this invention are useful as muscle relaxants.

The following examples illustrate the in- 45 vention:

Example 1.

Preparation of the dibromide of bis-[8-(Nmethyl - tetrahydro - papaverino)ethyl] malonate.

1.7 Gm. of laudanosine, 0.5 g. of β-bromoethyl malonate, and 20 ml, of dry benzene were refluxed together for 300 hours. The product which separated hardened on cooling and was removed by filtration, washed with benzene and dried. The solid residue was purified by dissolving in anhydrous ethanol

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and adding the solution thus formed drop by drop to mechanically stirred ether. The precipitate was filtered off and reprecipitated in

a similar manner. The product was a creamcoloured microcrystalline powder.

 $C_{40}H_{64}O_{12}N_2Br_2$ requires N 2.7% Br 15.5% found N 2.7% Br 15.3%

Example 2.

Preparation of the dibromide of bis-[\beta-(Nmethyl - tetrahydro - papaverino)ethyl] succinate.

3.2 Gm. of laudanosine, 1.0 g. of β -bromoethyl succinate and 25 ml. of dry benzene were refluxed together for 134 hours. The product of the reaction was a thick gum from which the benzene was removed by

decantation. The residue was washed three times with hot benzene by decantation, dried and dissolved in methanol. The solution thus obtained was added drop by drop to mechanically stirred ether. The precipitate was filtered off and was further purified by twice reprecipitating in a similar manner. The product was a cream-coloured microcrystalline powder.

 $C_{50}H_{66}O_{12}N_{2}Br_{2}$ requires N 2.7% Br 15.3% found N 2.7% Br 15.8%

EXAMPLE 3.

Preparation of the dibromide of bis-[\beta-(N-30 methyl - tetrahydro - papaverino)ethyll

1.8 Gm. of laudanosine, 0.5 g. of β bromoethyl oxalate and 30 ml. of dry benzene were refluxed together for 416 hours. The product which separated hardened on cooling, the benzene was removed by decantation and

the residue was washed three times with hot benzene and dried. The solid residue was purified by dissolving it in anhydrous ethanol and adding the solution thus formed drop by drop to mechanically stirred ether. The precipitate was filtered off and twice reprecipitated in a similar manner. The product was a cream-coloured powder.

C₄₆H₆₂O₁₂N₂Br₂ requires N 2.75% Br 15.7% found N 3.0% Br 16.0%

EXAMPLE 4. Preparation of the dibromide of bis- $[\beta$ -(Nmethyl - tetrahydro - papaverino)ethyl]

glutarate.

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3.1 Gm. of laudanosine, 1.0 g. of β bromoethyl glutarate and 40 ml. of dry benzene were refluxed together for 425 hours. After removal of the benzene by decantation

the gummy residue was washed three times 55 with hot benzene and dried. The residue was purified by dissolving in anhydrous ethanol and adding the solution thus formed drop by drop to mechanically stirred ether. The precipitate was filtered off and reprecipitated twice in a similar manner. The product was a cream-coloured powder.

C₅₁H₄₈O₁₂N₂Br₂ requires N 2.6% Br 15.1% found N 2.65% Br 14.5%

EXAMPLE 5.

Preparation of the dibromide of bis-[3-(Nmethyl - tetrahydro - papaverino)ethyl]

1.4 Gm. of laudanosine, 0.5 g. of 3-70 bromoethyl adipate and 20 ml. of dry benzene were refluxed together for 950 hours. The product was a thick gurn from which the benzene was removed by decantation and the

residue washed three times with hot benzene and dried. The residue was purified by dissolving in anhydrous ethanol and adding the solution thus formed drop by drop to mechanically stirred ether. The precipitate was filtered off and reprecipitated twice in a similar manner. The product was a creamcoloured powder.

C₅₀H₁₉O₁₂N₂Br₂ requires N 2.6% Br 14.9% found N 2.85 // Br 14.6 //

Preparation of the dibromide of bis-[8-(Nethyl - tetrahydro - papaverino)ethyl]

2.9 Gm. of N-ethyl-tetrahydropapaverine, 1.0 g. of β-bremeethyl adipatr and 40 ml. of dry benzene were refluxed together for 1400 hours. After removal of the benzene by decantation the guminy residue was washed three times with hot benzene and dried. The residue was purified by dissolving in

Inhydrous cil : I and adding the solution and reprecipitated twice in a similar manner. thus formed drop by drop to in chanically chirred other. The precipitate was filtered off

The product was a cream-coloured powder.

 $\begin{array}{ccccc} C_{54}H_{74}O_{12}N_{1}Br_{2} & requires & N & 2.5\% & Br & 14.45\%, \\ & & found & N & 2.7\% & Br & 15.0\%. \end{array}$

ENAMPLE 7.

Preparation of the dibromide of bis-[\beta-(Ncthyl - tetrahydro - papaverino)ethyl] malonate.

1.8 Gm. of N-ethyl-tetrahydro-papaverine, 0.5 g. of β -brome-ethyl malonate and 20 ml. of dry benzene were refluxed together for 1500

15 hours. The benzene was removed by decantation from the thick gummy residue which

was then washed three times with hot benzene and dried. The residue was purified by dissolving in anhydrous ethanol and adding the solution thus formed drop by drop to mechanically stirred ether. The precipitate was filtered off and twice reprecipitated in a similar manner. The product was a creamcoloured powder.

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C₁₁H₆₈O₁₂N₂Br₂ requires N 2.6% Br 15.1% N 2.7% Br 15.8% found

EXAMPLE 8.

Preparation of the dibromide of bis-[7-(Nmethyl - tetrahydro - papaverino)propyl]

5.4 Gm. of laudanosine, 1.25 g. of γ bromopropyl oxalate and 35 ml. of dry benzene were refluxed together for 310 hours. After removal of the benzene by decantation, a cream-coloured powder.

the gummy residue was washed three times with hot benzene and dried. The residue was purified by dissolving in anhydrous ethanol and adding the solution thus formed drop by drop to mechanically stirred other. The precipitate was filtered off and reprecipitated twice in a similar manner. The product was

C₂₆H₆₆O₁₂N₂Br₂ requires N 2.7% Br 15.3% found N 2.7% Br 14.75%

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EXAMPLE 9. Preparation of the dibromide of bis-[7-(Nmethyl - tetrahydro - papaverino)propyl]

1.8 Gm. of laudanosine, 0.58 g. of γ -50 bromopropyl malonate and 30 ml. of dry benzene were refluxed together for 520 hours. After removal of the benzene by de-

cantation the gummy residue was washed three times with hot benzene and dried. The solid was purified by dissolving in anhydrous ethanol and adding the solution thus formed drop by drop to mechanically stirred ether. The precipitate was filtered off and reprecipitated twice in a similar manner. The product was a cream-coloured powder.

C₅₁H₆₆O₁₂N₂Br₂ requires N 2.6% Br 15.1% found N 2.6% Br 15.0%

Example 10.

Preparation of the diperchlorate of bis- β -(Nmethyl - tetrahydro - papaverino)ethyl]

0.18 Gm. of the dibromide of bis- $[\beta$ -(Nmethyl - tetrahydro - papaverino)ethyl] malonate, dissolved in 10 ml. of water was

filtered and added dropwise to a solution of 0.1 g. of sodium perchlorate in 5 ml. of water. The precipitate was removed by filtration, washed with water, dried and recrystallised from dimethyl formamide and ether. The product was a buff-coloured compound.

Example 11.

Preparation of the dinitrate of bis-[3-(Nmethyl - tetrahydro - papaverino)ethyl] oxalate.

0.07 Gm, of the dibromide of bis-16-(Nmethyl - tetrahydro - papaverino)ethyll oxalate, dissolved in 2 ml. of anhydrous ethanol was added dropwise to a solution of

0.012 g. of silver nitrate in 16 ml. of anhydrous ethanol. The reaction mixture was refluxed for 30 minutes, allowed to cool and filtered. An excess of anhydrous ether was added to the filtrate and the precipitate removed by filtration. The product was purified by redissolving in anhydrous ethanol and adding the solution thus formed drop by drop

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to in charactery stitued other. The procipitite was filtered off and reprecipitated out in a similar manner. The product was a leff-coloured powder.

C₆₈H₆₂O₁₆N₄ requires N.5.76 / found N.5.75 //

ENAMPLE 12.

Preparation of the diperchlorate of bis-[7-(N-methyl - tetrahydro - papaverino)propyl]

10 oxalate.

1.0 Gm. of the dibromide of bis-je/N-mothyl - 1 trahydro - papaverind/propyll or date, discolved in 15 ml. of water was added dropwise to a solution of 0.24 gm. of sediam perchlerate in 15 ml. of water. The precipitate was removed by filtration, washed with water, dried, dissolved in anhydrous actione, and reprecipitated with anhydrous ethanol. After a further purification in a similar manner the product was a yellow 20 powder.

EXAMPLE 13.

25 Preparation of the di-iodide of bis-[7-(N-methyl - tetrahydro - papaverine)propyl] oxalate.

4.7 Gm. of tetrahydro - papaverine hydriodide was added to an excess of 2 N sodium hydroxide solution, and the liberated base completely extracted with benzene. The combined benzene extracts were washed with water and dried over anhydrous magnesium sulphate. The extract was separated by filtration and the colored research.

5 tion and the solvent removed by distillation. The remaining light brown oil was dissolved in 50 ml. of anhydrous acctone. 1.52 Gm. of anhydrous potassium carbonate and 1.66 gm. of bis-(γ-bromopropyl)-oxalate, dissolved in

50 ml. of anhydrous acetone, were added to the acetone solution of tetrahydro-papaverine and refluxed together for 104 hours. The solution was cooled and separated by filtration. The solvent was removed by distillation under reduced pressure. Bis-[γ-(tetrahydro-papaverino)propyl] oxalate was obtained as a light brown oil (4.5 gm)

light brown oil (4.5 gm.).

1 Ml. of methyl iodide was added to a solution of 2.25 gm. of bis-[\gamma-(N-tetrahydro-papaverino)propyl] oxalate in 10 ml. of anhydrous acetone. The solution was allowed to stand for 1.5 hours and then refluxed for 1.5 hours. The oil which separated crystallised after the addition of anhydrous ether. The product was a pale yellow powder.

The dibromide of bis-[7-(N-methyl-tetrahydro-papaverino)propyl] oxalate when administered intravenously to mice in effective doses produced paralysis which was not

preceded nor followed by excitation. The paralysing activity of the drug was determined in mice and the results of these experiments are summarised in Table I:—

TABLE I

Index	No. of expts.	Mean Value mg./kg.	Range mg./kg.		
ED 50	10	1.61	1.38 — 1.95		
ED 50	6	5.31	4.76 — 6.46		

The compounds of the present invention were examined by intravenous administration to cats, maintained by artificial ventilation and prepared for recording the isometric twitch of the tibialis anterior muscle in

response to stimulation of its motor nerve. The duration of activity of the neuro muscular blocking action was compared with that of suxamethonium chloride. The results of these experiments are given in Table II:—

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TABLE H

Compound in which, R, m, n and X of the general formula have the values:				No. of cats	Duration of action as compared with suna- methonium chloride(==1)		
R	m	n	Х				
CH3	2	2	Br	3	5.4		
CH_3	2	1	Br	8	2.6		
CH ₃	3	1	Br	3	9.0		
CH ₃	3	0	Br	8	0.5		

In each case Neostigmine was found to be an effective antagonist. The cumulative action of suzamethonium chloride and the dibromide of bis- $[\gamma-(N-methyl-tetrahydro-papaverino)-propyl]$ oxalate were compared in three cats

in which series of successive equal doses of one substance were given at equal intervals of time. The results of this experiment are given in Table III.

TABLE III

Effect	Suxamethonium chloride 50 µg/kg.				dibromide of bis-[γ-(N-methyl-tetrahydropapaverino)propyl] oxalate 3 mg./kg.			
	Ist dose	2nd dose	3rd dose	4th dose	1st dose	2nd dose	3rd dose	4th dose
Depression tibialis twitch (%)	69	83	. 88	94	69	65	74	75
Duration to 75% recovery (sec.)	190	290	370	340	130	120	150	140

From these results it will be seen that the compounds of the present invention have no significant cumulative effect.

WHAT WE CLAIM IS:—

1. Diquaternary salts of bis- $[\omega$ -(tetra-hydro-papaverino)alkyl] esters of aliphatic dicarboxylic acids of the general formula:

where R is a lower alkyl group containing not more than 6 carbon atoms; X is an anion; m is 2 or 3 and n is 0, 1, 2, 3 or 4.

2. The dibromide of bis-[γ-(N-methyl-tetrahydro-papaverino)propyl]oxalate.

3. The di-iodide of bis-[\gamma-(N-methyl-tetra-

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hydro-p: paverino)propyl] exalate.

4. A process for preparing the compounds of the general formula specified in claim 1 where X is bromine and which comprises refluxing an excess of an N-alkyl tetrahydropapaverine with an w-bromalityl dicarboxylate in an inert solvent for a prolonged period.

5. A process for preparing the compounds claimed in any one of the preceding claims 1 to 3 which comprises reacting an ω-bromoalkyl dicarboxylate with tetrahydro-papaverine in the presence of an acid-binding agent, and treating the product obtained with at least 2 molecular proportions of an alkyl halide or

6. A process for preparing the compounds claimed in claim 1 substantially as described with reference to any one of the Examples.

7. The compounds claimed in claim I when produced by the process claimed in any one of claims 4 to 6.

ELKINGTON AND FIFE, Consulting Chemists and Chartered Patent Agents,

Bank Chambers, 329, High Holborn, London, W.C.1, Agents for the Applicants.

PROVISIONAL SPECIFICATION

Tetrahydropapaverine Derivatives and their preparation

We, Allen & Hanburys Limited, a British Company, of Three Colts Lane, Bethnal Green, London, E.2, do hereby declare this invention to be described in the following statement: -

This invention relates to new heterocyclic

compounds.

The compounds of the present invention are diquaternary salts of bis-[ω-(tetrahydropapaverino)alkyl] esters of aliphatic dicarboxylic acids of the general formula:

where R is a lower alkyl group containing not 35 more than 6 carbon atoms; X is an anion; m is 2 or 3 and n is 0, 1, 2, 3 or 4.

The present invention also includes a process for preparing the compounds of the present invention, which comprises refluxing 40 an excess of an N-alkyl tetrahydro papayerine with an ω-bromalkyl dicarboxylate in an inert solvent for a prolonged period, e.g., several days. The inert solvent may, for example, be an aromatic hydrocarbon such as benzene.

The present invention further includes a process for preparing the compounds of the present invention which comprises reacting an o-bromoalkyl dicarboxylate with tetrahydro papaverine, and treating the product obtained 50 with at least 2 molecular proportions of an alkyl halide or sulphate.

The compounds of this invention are useful

as muscle relaxants.

The following examples illustrate the invention:

EXAMPLE 1.

Preparation of the dibromide of bis-[β -(Nmethyl - tetrahydro - papaverino)ethyl] malonate.

1.7 Gm. of laudanosine, 0.5 g. of β - of bromoethyl malonate and 20 ml. of dry benzene were refluxed together for 300 hours. The product which separated hardened on cooling and was removed by filtration, washed with benzene and dried. The solid residue was 6 purified by dissolving in anhydrous ethanol and adding the solution thus formed drop by drop to mechanically stirred ether. The precipitate was filtered off and reprecipitated in a similar manner. The product was a creamcoloured microcrystalline powder.

C45H64O12N2Br2 requires N 2.7% Br 15.5% found N 2.7 / Br 15.3 %

Example 2. Preparation of the dibromide of bis-[\beta-(N-

succinate.

3.2 Gm. of laudanosine, 1.0 g. of β methyl - tetrahydro - papaverino)ethyl] bromoethylsuccinate and 25 ml. of dry

863,717 househe were reflered together for 134 Louis. obtained was added drop by drop to receiving-15 cally stirred other. The precipitate was The product of the relation was a thick gumrunds filtered off and was further purified by twice from which the beaze, a was removed by deribed reprecipitating in a similar manner. The procantation. The residue was washed three times les. with hot benzene by decantation, dried and doct was a cream-coloured microcrystalline when dissolved in methanol. The solution thus powder. . one 20 $\begin{array}{cccc} C_{\rm ac} H_{\rm bc} O_{12} N_{\rm c} B r_{\rm c} & {\rm requires} & N & 2.7\% & Br & 15.3\% \\ & & found & N & 2.7\% & Br & 15.8\% \end{array}$ tent cantation and the residue was washed three EXAMPLE 3. 15 Preparation of the dibromide of bis-[\$\beta\$-(Ntimes with hot benzene and dried. The solid methyl - tetrahydro - papaverino)ethyl] residue was purified by dissolving it in anhydrous ethanol and adding the solution oxalate. 1.8 Gm. of laudanosine, 0.5 g. of β -bromoethyl oxalate and 30 ml. of dry thus formed drop by drop to mechanically stirred ether. The precipitate was filtered off benzene were refluxed together for 416 hours. and twice reprecipitated in a similar manner. The product which separated hardened on The product was a cream-coloured powder. cooling, the benzene was removed by deation C₁₈H₆₂O₁₂N₂Br₂ requires N 2.75% Br 15.7% found N 3.0% Br 16.0% -orb; 30 di-Example 4. the gummy residue was washed three 35 Preparation of the dibromide of bis- $[\beta$ -(Ntimes with hot benzene and dried. The methyl - tetrahydro - papaverino)cthyl] residue was purified by dissolving in glutarate. anhydreus ethanol and adding the solution 3.1 Gm. of laudanosine, 1.0 g. of β -bromoethyl glutarate and 40 ml. of dry thus formed drop by drop to mechanically stirred ether. The precipitate was filtered off benzene were refluxed together for 425 hours. and reprecipitated twice in a similar manner. After removal of the benzene by decantation The product was a cream-coloured powder. C₅₁H₆₅O₁₂N₂Br₂ requires N 2.6% Br 15.1% found N 2.65% Br 14.5% 50 residue washed three times with hot benzene Example 5. Preparation of the dibromide of bis-[β -(Nand dried. The residue was purified by dismethyl - tetrahydro - papaverino)ethyl] solving in anhydrous ethanol and adding the solution thus formed drop by drop to mechani-55 adipate. 1.4 Gm. of laudanosine, 0.5 g. of β incally stirred ether. The precipitate was filtered 55 bromoethyl adipate and 20 ml. of dry benzene off and reprecipitated twice in a similar were refluxed together for 950 hours. The manner. The product was a cream-coloured $\cdot (N$ product was a thick gum from which the powder. hyl] benzene was removed by decantation and the B-60 C₅₂H₇₀O₁₂N₂Br₂ requires N 2.6% Br 14.9% found N 2.85% Br 14.6% dry 70 urs. on three times with hot benzene and dried. The Preparation of the di-bromide of bis- $[\beta-(N$ ihed ethyl - tetrahydro - papaverino)ethyl] residue was purified by dissolving in anhydrous was 65 ethanol and adding the solution thus formed adipate. anol 2.9 Gm. of N-ethyl-tetrahydropapaverine, drop by drop to mechanically stirred ether. → by 75 1.0 g. of β -bromoethyl adipate and 40 ml. of The precipitate was filtered off and reprecipipredry benzene were refluxed together for 1400 tated twice in a similar manner. The product i in hours. After removal of the benzene by dewas a cream-coloured powder. 70 21T:cantation the gummy residue was washed C₅₄H₇₄O₁₅N₂Br₂ requires N 2.5% Br 14.45% found N 2.7% Br 15.0% malonate. Example 7.

Preparation of the dibromide of bis-[\beta-(Nethyl - tetrahydro - papaverino)ethyl]

1.8 Gm. of N-ethyl-tetrahydro-papaverine, 0.5 g. of β -bromoethyl malonate and 20 ml.

of dry bename were refluxed together for 150c hours. The benzene was ren, ved by decantation from the thick gummy residue which was then washed three times with hot 5 benzene and dried. The residue was purified by dissolving in anhydrous ethanol and

adding the solution thus fermed drop by drop to mechanically stirred other. The precipitate was filtered off and twice reprecipitated in a similar manner. The product was a creamcoloured powder.

EXAMPLE 8.

15 Preparation of the dibromide of bis-[γ-(Nmethyl - tetrahydro - papaverino)propyl}

5.4 Gm. of laudanosine, 1.25 g. of γ bromopropyl oxalate and 35 ml. of dry 20 benzene were refluxed together for 310 hours. After removal of the benzene by decantation

the gummy residue was washed three times with hor benzene and dried. The residue was purified by dissolving in anhydrous ethanol and adding the solution thus formed drop by drop to mechanically stirred ether. The precipitate was filtered off and reprecipitated twice in a similar manner. The product was a cresm-coloured powder.

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C .. H . O 12 N 2 Br 2 requires N 2.7 % Br 15.3%

found N 2.7 6 Br 14.75%

EXAMPLE 9.

Preparation of the dibromide of bis- $[\gamma-(N$ methyl - tetrahydro - papaverino)propyl] malonate.

1.8 Gm. of laudanosine, 0.58 g. of γ bromopropyl malonate and 30 ml. of dry benzene were refluxed together for 520 hours. After removal of the benzene by decantation

the gummy residue was washed three times with hot benzene and dried. The solid was purified by dissolving in anhydrous ethanol and adding the solution thus formed drop by drop to mechanically stirred ether. The precipitate was filtered off and reprecipitated twice in a similar manner. The product was a cream-coloured powder.

 $C_{s1}H_{6s}O_{12}N_{2}Br_{2}$ requires N 2.6% Br 15.1% found N 2.6% Br 15.0%

EXAMPLE 10.

Preparation of the di-perchlorate of bis-1\beta-(Nmethyl - tetrahydro - papaverino)ethyl] malonate.

0.18 Gm. of the dibromide of bis- $[\beta$ -(N-55 methyl - tetrahydro - papaverino)ethyl] malonate, dissolved in 10 ml. of water was

filtered and added dropwise to a solution of 0.1 g, of sodium perchlorate in 5 ml, of water. The precipitate was removed by filtration, washed with water, dried and recrystallised 60 from dimethyl formamide and ether. The product was a buff-coloured compound.

EXAMPLE 11.

Preparation of the dinitrate of bis-[\beta-(Nmethyl - tetrahydro - papaverino)ethyl]

0.07 Gm. of the dibromide of bis-[β -(N-70 methyl - tetrahydro - papaverino)ethyl] oxalate, dissolved in 2 ml. of anhydrous ethanol was added dropwise to a solution of 0.012 g. of silver nitrate in 16 ml. of anhydrous ethanol. The reaction mixture was refluxed for 30 minutes, allowed to cool and filtered. An excess of anhydrous ether was added to the filtrate and the precipitate removed by filtration. The product was purified by redissolving in anhydrous ethanol and adding the solution thus formed drop by drop to mechanically sucred ether. The precipitate was filtered off and reprecipitated once in a

similar manner. The product was a buffcoloured powder.

C46H62O15N4 requires N 5.76% found N 5.75%

EXAMPLE 12.

Preparation of the di-perchlorate of bis-[7-(Nmethyl - tetrahydro - papaverino)propyl] oxalate.

1.0 Gm. of the dibromide of bis-[7-(Nmethyl - tetrahydro - papaverino)propyl] oxalate, dissolved in 15 ml. of water was added dropwise to a solution of 0.24 gm. of sodium perchlorate in 15 ml. of water. The precipitate was removed by filtration, washed with water, dried, dissolved in anhydrous acetone, and reprecipitated with anhydrous ethanol. After a further purification in a

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in a

C₅₀H₆₀O₅₀N₂Cl₆ to paires N 2.6% Cl 6.5% found N 2.6% Cl 6.1%

ENAMPLE 13.

Preparation of the diiodide of bis-[7-(N-methyl - tetrahydro - papaverino)propyl] oxalate.

cimilar manner the product was a yellow powder.

4.7 Gm. of tetrahydropapaverine hydriodide
was added to an excess of 2 N sodium
hydroxide solution, and the liberated base
completely extracted with benzene. The combined benzene extracts were washed with
water and dried over anhydrous magnesium
sulphate. The extract was separated by
filtration and the solvent removed by distillation. The remaining light brown oil was dissolved in 50 ml. of anhydrous acetone. 1.52

Gm. of anhydrous potassium carbonate and 20 1.66 gm. of bis-(7-bromopropyl)oxalate, dis-

solved in 50 ml. of anhydrous acetone, were added to the acetone solution of tetrahydropapaverine and refluxed together for 104 hours. The solution was cooled and separated by filtration. The solvent was removed by distillation under reduced pressure. Bis-[γ-(tetrahydropapaverino)propyl] oxalate was obtained as a light brown oil (4.5 gm.).

QUATERNISATION.

1 Ml. of methyl iodide was added to a solution of 2.25 gm. of the base in 10 ml. of anhydrous acetone. The solution was allowed to stand for 1.5 hours and then refluxed for 1.5 hours. The oil which separated crystallised after the addition of anhydrous ether. The product was a pale yellow powder.

C₅₆H₆₆O₁₂N₂I₂ requires N 2.45% I 22.2% found N 2.5% I 22.7%

ELKINGTON AND FIFE,
Consulting Chemists and Chartered Patent
Agents,
Bank Chambers, 329, High Holborn,
London, W.C.1,
Agents for the Applicants.

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